## REMARKS

Claims 32-47 are pending for prosecution. Claims 33-35 have been cancelled and claims 32, 36, 38, 40, 42 and 43 have been amended.

Support for amended claim 32 can be found as follows: the terms "modified" and "endonuclease" are found throughout the application. The application refers to a DNA cleaving enzyme exemplified by T-odd phage endonucleases in [0092]. Mutation is defined as meaning "deletion, substitution or addition of one or more amino acids in the enzyme" [0094]. "[A]ltered enzyme activity" is described in [0095 and 0096]. No new subject matter is believed to have been added. It is believed that the presently amended claim 32 and dependent claims more distinctly describe the invention. The Examiner is respectfully requested to enter the amended claims.

Applicants thank the Examiner and the Supervisory Examiner for the opportunity of an in-person interview in November 2009 at the United States Patent and Trademark Office. At that time, Applicants discussed the Examiner's rejections with respect to written description, emphasizing to the Examiner the surprising discovery of the significance of modifications in the specific short sequence that formed the β-bridge. Changes in the β-bridge alone resulted in altering the relative positions of the catalytic domains with the unexpected effect of changing the activity of the endonucleases. In addition, Applicants pointed out the highly conserved structure of T-odd phage endonucleases having two catalytic domains separated by a short β-bridge. After additional discussion of acceptable claim

structures during the interview, Applicants put forward a claim which received favorable consideration and is now presented as amended claim 32 for further consideration by the Examiner. The Supervisory Examiner pointed out that 24 examples seemed to be sufficient to support the scope of the claim given the specific character of the β-bridge.

Rejection under 35 U.S.C §102

The rejection of claims 32, 40, 41 and 42 prior to amendment as anticipated under 35 U.S.C. §102 by the phage amino acid sequence listed by Beck is moot as the present claims require a modified recombinant protein with altered activity. The Beck phage T3 sequence predicted to be an endonuclease was not cloned or modified and no motivation was provided to do so. Moreover, without the present teaching, a person of ordinary skill in the art might expect problems in cloning the "predicted" T3 endoribonuclease due to suggested toxic nuclease activity in view of the sequence similarities with the toxic T7 Endo I (unmodified).

Rejection under 35 U.S.C §103

Rejection of claim 44 prior to amendment on the basis of obviousness in view of Beck is now moot for the reasons provided above.

Rejection under 35 U.S.C §112 1st paragraph

The Examiner has calculated a number for possible variants of $10^{166}$ which is greater than the number of atoms in our planet according to a mathematician at New England Biolabs. However, as discussed in the interview, the present claim now clearly presents only

a small number of clearly defined endonucleases having a well-defined structure and a small number of amino acids that are the target of modification. The target of the modification is described for example in the application [0094].

The Examiner stated that "the specification does not provide those structural features which are associated with the recited activity". However, the application described in numerous ways that changes in the β-bridge give rise to altered activity. For example:

> genetically changing the distance between the two catalytic centers by introducing mutations into the bridge site of the protein." [0098];
>
> The reciprocal stereo-geometric positions of the two catalytic centers in an enzyme of the above class can be changed by introducing mutations into the bridge without changing the catalytic centers per se using genetic or biochemical means" [0094];
>
> Mutations in the bridge portion of the enzyme resulted in shifting the enzyme activity...." [0095] also see [0096];
>
> Surprisingly, nucleotide substitutions in the β-bridge that were of variable length (single amino acid, dipeptide, tripeptide, tetrapeptide) negatively charged, positively charged or neutral in charge flexible in structure or inflexible in structure revealed altered enzyme activities of the type described herein" [0098]
>
> Approximately 24 β-bridge site mutants were generated. The proteins were purified and characterized. All the mutations in some way altered the activity profile of the enzyme... [0099]

Figure 12 shows the confirmation of the two catalytic domains and the β-bridge for SEQ ID NO:12. In the response dated June 17, 2009, Applicants submitted Appendix I showing the reproducible structure by comparing 2 different T-odd phages.

The claims have now been amended such that they more clearly recite a mutation in the β-bridge giving rise to altered enzyme activity.

Applicants assert that the claims are now commensurate in scope with the description in the above application and a person of ordinary skill in the art could readily understand the description of the claimed compositions and would be enabled to make the claimed compositions.

## CONCLUSION

Applicants respectfully submit that this case is in condition for immediate allowance. Early and favorable consideration leading to prompt issuance of this Application is earnestly solicited.

Applicants petition for a three-month extension of time and attach a notice of appeal. Applicants authorize that the fees for the extension and notice totalling $825 be charged to Deposit Account No. 14-0740. Applicants authorize that any deficiencies that may be due be charged to the same Account.

Respectfully submitted,

NEW ENGLAND BIOLABS, INC.

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*/Harriet M. Strimpel/*
Harriet M. Strimpel D.Phil.
(Reg. No.: 37,008)
Customer No.: 28986
Attorney for Applicant
240 Country Road
Ipswich, Massachusetts 01938
(978) 380-7373